



SDMS Doc ID 165688

## **Status of Recommended Studies NTP PWG: Thyroids**

- **Objective: Evaluate thyroids from 2/99 data with new and consistent scoring system & nomenclature**
  - Likely impact on dose-response
  - Will be applied to “effects” study for additional endpoints @ identified PK critical timepoints
- **Data due: Report to NCEA early May 2000**

## **Status of Recommended Studies “Effects” Protocol**

- **Objectives:**
  - Refine understanding of effect in thyroid and evaluate brain @ critical PK time points
  - Better brain morphometry — NIEHS consult
  - Correlate with additional hormone analyses to refine dose-response
  - Obtain rat Seg II guideline developmental data
- **Data due: June 2000**

### **Status of Recommended Studies Repeat Motor Activity**

- **Objective: Decrease variability in key neurodevelopmental measures**
  - Potential co-critical effect
  - Equipment appropriate to neonatal pups
  - Additional hormone analyses
  - USN facility at WPAFB
- **Data due: Report to NCEA June 2000**

### **Status of Recommended Studies Repeat Immunotoxicity**

- **Objective: Repeat SRBC assay and add delayed-type hypersensitivity (DTH) assay**
  - Critical to characterization of humoral immunity
  - DTH indicated by initial data
  - Impact on evaluation of all previous immunotoxicity data
- **Data due: Report to NCEA June 2000**

### **Status of Recommended Studies Pharmacokinetics in Rats**

- **Objective: Obtain data @ critical time points in pregnant & lactating dams, fetuses, neonates**
  - Critical to evaluate dose-response of iodide uptake inhibition; single and repeat dosage regimen
  - Additional hormone analyses
  - Critical to ascertain fetal compartment kinetics as insight e.g., on PND5 thyroid effects
  - Inform interspecies extrapolation
- **Data due: Initial adult model March 2000; lactating and fetal initial model in June 2000**

### **Status of Recommended Studies Pharmacokinetics in Humans**

- **Objective: Obtain data to evaluate single versus repeated dose on iodide uptake, hormone levels**
  - Critical to interspecies extrapolation
  - Different studies via contract to either AFRL (Phase I) or PSG (Phase II)
- **Data due: Initial model June 2000; refinements pending IRB; data from Phase II begin April 2000**

## **Status of Recommended Studies**

### **Interlaboratory Hormone Analysis Validation**

- **Objective: Decrease variability in hormone analyses across studies**
  - Original February 1999 data set
  - Ongoing aspect of all studies
- **Data due: Draft report March 2000; final May 2000**

## **Revised Harmonized Oral Human Health Benchmark ("RfD")**

- Data across comprehensive array of endpoints to establish target tissue
- Mechanistically-motivated special studies to characterize critical dose-response relationships
- Harmonized nonlinear approach to both cancer and noncancer assessment based on mode of action
- New "RfD" estimate at 0.0009 mg/kg-day translates to approximately 2-fold higher guidance level (32 ppb)
- Future refinements with new data, PWG results, and development of PBPK dosimetry model
- Due to these remaining uncertainties, ORD has recommended that original RfD range of 0.0001 to 0.0005 mg/kg-day be used in interim

